Research Article

Development Of Smart Thermo-Responsive Polymer Blends For Temperature-Triggered Release Of Poorly Water Soluble Nsaids

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ABSTRACT:

Non-steroidal anti-inflammatory drugs' (NSAIDs) weak water solubility sometimes causes poor absorption, inconsistent therapeutic response, and recurrent doses. Drug delivery via clever thermo-responsive polymer systems seems promising. This study developed thermo-responsive polymer blends to regulate the release of a non-water-soluble NSAID. PNPAM, PEG, and HPMC were mixed to make thermo-responsive polymer blends via solvent casting and cross-linking. Water-insoluble celecoxib was chosen as the model NSAID. Drug loading, entrapment efficiency, morphology, thermal properties, gelation temperature, and in vitro drug release were characterised at 25°C, 37°C, and 40°C. To determine drug-polymer compatibility, FTIR and DSC were utilised. The low critical solution temperature (LCST) of 34.8 ± 0.6°C makes the optimised thermo-responsive formulation (TRP-4) acceptable for physiological temperature-triggered drug release. The formulation showed 12.4 ± 0.8% drug loading capacity and 89.6 ± 2.7% entrapment efficiency. According to swelling studies, thermo-induced polymer contraction reduced swelling ratio from 412 ± 18% at 25°C to 176 ± 11% at 40°C. Over 24 hours, controlled drug release studies at 25°C, 37°C, and 40°C yielded 31.4 ± 2.1%, 68.7 ± 3.5%, and 92.3 ± 4.2%, respectively. FTIR and DSC investigations confirmed celecoxib had been absorbed into the polymer matrix and that there were no drug-polymer interactions. These SEM images showed a consistently porous structure with temperature-responsive releasing behaviour. Drug release kinetics were best fit by the Korsmeyer-Peppas model (R^2 = 0.987), indicating diffusion regulation rather than anticipated mechanism. Its drug entrapment, thermal responsiveness, and controlled release qualities allowed the thermo-responsive polymer mix to release celecoxib at a temperature. Smart thermo-responsive polymer systems may increase the therapeutic efficacy and dispersion of non-water-soluble NSAIDs, according to these findings.

Keywords: Thermo-responsive polymers; Temperature-triggered drug release; Poly(N-isopropylacrylamide); Celecoxib; Smart drug delivery system; Polymer blends.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) significantly aid in the management of inflammation, pain, arthritis, musculoskeletal issues, and postoperative conditions. A multitude of nonsteroidal anti-inflammatory medicines (NSAIDs) exhibit restricted therapeutic efficacy, oral bioavailability, and dissolution rates owing to their inadequate water solubility; yet, these medications are widely utilised in clinical practice [1, 2]. When a medication exhibits low solubility, it typically necessitates administering larger doses more frequently, hence heightening the probability of experiencing adverse effects such as gastrointestinal discomfort, renal impairment, and cardiovascular issues. Consequently, it is imperative for pharmaceutical scientists to concentrate on developing innovative drug delivery systems that enhance the solubility of NSAIDs, which exhibit limited water solubility, and facilitate regulated release [3, 4].

Stimuli-responsive polymers, sometimes referred to as smart polymers, provide a fascinating material for the advancement of improved drug delivery systems. The extraordinary characteristic of these polymers is their ability to respond to environmental stimuli such as light, magnetic fields, pH, temperature, and ionic strength through reversible physicochemical transformations [5]. Temperature is notable among these stimuli due to its significant controllability and its remarkable resemblance to the physiological and pathological conditions encountered by the human body. Thermo-responsive polymers facilitate site-specific and regulated drug release by altering their swelling characteristics, hydrophilicity, and molecular configuration in response to temperature fluctuations [6].

Due to its distinctly established lower critical solution temperature (LCST) around physiological temperature, poly(N-isopropylacrylamide) (PNIPAM) has been examined more extensively than many other thermo-responsive polymers. Above its lower critical solution temperature, PNIPAM undergoes a phase transition that restricts its water absorption and causes its polymer chains to contract, whereas below this temperature, it remains hydrated and expanded [7, 8]. This unique attribute enables the development of drug delivery systems that may modify their drug release properties in reaction to temperature fluctuations. However, integrating PNIPAM-based systems with hydrophilic polymers such as PEG and HPMC can significantly enhance their mechanical properties and drug-loading capabilities [9].

Polymer mixing is an effective and versatile technique for tailoring the physicochemical characteristics of drug delivery systems. The incorporation of PEG improves hydrophilicity, biocompatibility, and swelling characteristics, whilst HPMC offers advantages such as matrix integrity, mucoadhesion, and prolonged drug release [10, 11]. A thermo-responsive matrix exhibiting improved drug encapsulation efficiency, release kinetics, and temperature sensitivity can be synthesised through the synergistic combination of these polymers. The controlled release under physiological conditions and enhanced drug distribution inside the polymer matrix render these intelligent polymer blends optimal for delivering poorly water-soluble medicines [12].

Recent advancements in controlled drug delivery have concentrated on the creation of devices capable of administering drugs in response to localised physiological alterations. The heightened metabolic activity and enhanced blood circulation associated with inflammatory disorders might result in localised temperature elevations. To enhance therapeutic effectiveness and minimise systemic exposure, thermo-responsive drug delivery systems can utilise this phenomenon for temperature-activated release. Moreover, controlled release devices can maintain therapeutic drug levels for extended periods, resulting in patients needing to administer their prescription less frequently and increasing adherence to prescribed regimens [13, 14].

This investigation aimed to formulate and characterise intelligent thermo-responsive polymer blends consisting of PNIPAM, PEG, and HPMC for the temperature-mediated release of celecoxib, a representative poorly water-soluble NSAID. The structure, medication incorporation, entrapment efficacy, swelling characteristics, thermal transition behaviour, and in vitro release capabilities of the formulated products were evaluated at different temperatures. The findings of this research may assist in developing enhanced medicine delivery systems that react to stimuli, perhaps improving the management of inflammatory disorders and chronic pain [15, 16].

2. MATERIAL AND METHODS

2.1 Materials

NSAID Celecoxib, having a purity of ≥99%, was chosen as the model weakly water-soluble NSAID. Primary thermo-responsive polymer was poly(N-isopropylacrylamide) (PNIPAM) because to its lower critical solution temperature (LCST) approaching physiological temperature. Hydrophilic polymeric excipients PEG 6000 and HPMC K15M improved swelling, mechanical strength, and controlled drug release. Methylenebisacrylamide (MBA) was used as a cross-linking agent, and ammonium persulfate (APS) and TEMED were used as initiators and accelerators during polymerisation. HPLC-grade ethanol and methanol were employed for drug dissolution and analysis. Swelling and drug release tests used PBS (pH 7.4) as the dissolving media. All study chemicals and reagents were analytical or pharmaceutical grade and unpurified. The experiments employed double-distilled water.

2.2 Preparation of Thermo-Responsive Polymer Blends

A combination of solvent casting and free radical polymerisation was used to create thermo-responsive polymer blends. In a nutshell, PNIPAM was dissolved in distilled water while being constantly stirred by magnetic forces. The homogeneous polymeric solutions were prepared by adding PEG 6000 and HPMC K15M at preset ratios. Next, the cross-linking agent (MBA) was added, and then APS and TEMED were added to start the polymerisation process. The polymeric mixture was gradually added to the dissolved celecoxib in a small volume of ethanol while stirring constantly. Glass Petri dishes were used to cast the resultant solution, which was then left to polymerise at room temperature for 24 hours. After film formation, the polymer was dried at 40°C until a consistent weight was reached. Before further investigation, the films were dried and then sliced into uniform specimens. They were then stored in desiccators [17, 18].

2.3 Experimental Design and Optimization

The Box-Behnken design was used to construct 15 experimental runs, with 3 center-point replicates, in order to assess the individual, interaction, and quadratic effects of the factors that were chosen on the responses. In order to find the best conditions for formulation, mathematical models were built utilising multiple regression analysis and response surface methodology. The statistical significance of the created models was evaluated using analysis of variance (ANOVA), with a p-value less than 0.05 being deemed statistically significant [19].

- X_1: PNIPAM concentration (% w/v)
- X_2: PEG concentration (% w/v)
- X_3: Cross-linker (MBA) concentration (% w/v)

The dependent responses included:

- Y_1: Entrapment efficiency (%)
- Y_2: Swelling ratio (%)
- Y_3: Drug release at 40°C (%)

Design-Expert® software was utilized for statistical analysis and optimization of formulation parameters.

Table 1: Box–Behnken Design Matrix and Experimental Responses

Run	X_1 PNIPAM (% w/v)	X_2 PEG (% w/v)	X_3 MBA (% w/v)	Y_1 Entrapment Efficiency (%)	Y_2 Swelling Ratio (%)	Y_3 Drug Release at 40°C (%)
1	4.0	1.0	0.20	76.3 ± 2.1	382 ± 15	78.6 ± 3.1
2	8.0	1.0	0.20	82.5 ± 2.4	344 ± 14	84.3 ± 3.4
3	4.0	3.0	0.20	80.7 ± 2.3	401 ± 17	82.1 ± 3.3
4	8.0	3.0	0.20	87.4 ± 2.5	298 ± 12	89.7 ± 3.8
5	4.0	2.0	0.10	78.4 ± 2.2	425 ± 18	80.8 ± 3.2
6	8.0	2.0	0.10	85.6 ± 2.5	356 ± 15	87.2 ± 3.5
7	4.0	2.0	0.30	79.1 ± 2.3	318 ± 13	83.4 ± 3.1
8	8.0	2.0	0.30	88.2 ± 2.6	274 ± 11	91.5 ± 3.9
9	6.0	1.0	0.10	81.3 ± 2.4	398 ± 16	84.7 ± 3.3
10	6.0	3.0	0.10	84.8 ± 2.5	416 ± 17	88.4 ± 3.6
11	6.0	1.0	0.30	82.1 ± 2.4	302 ± 12	86.1 ± 3.4
12	6.0	3.0	0.30	87.3 ± 2.6	286 ± 11	90.6 ± 3.8
13	6.0	2.0	0.20	85.2 ± 2.6	365 ± 16	88.3 ± 3.5
14	6.0	2.0	0.20	84.9 ± 2.5	369 ± 15	88.0 ± 3.4
15	6.0	2.0	0.20	85.4 ± 2.7	367 ± 16	88.6 ± 3.5

2.4 Determination of Lower Critical Solution Temperature (LCST)

We used the cloud point method to find the LCST of the polymer blends that were synthesised. Under continuous stirring, the polymer dispersions were heated from 20 to 50 degrees Celsius at a rate of 1 degree Celsius per minute. Optical transmittance changes were tracked at 500 nm with a UV-visible spectrophotometer. We used the temperature at which transmittance dropped by half as our LCST [20].

2.5 Drug Loading and Entrapment Efficiency

Celecoxib was fully extracted by dissolving a defined quantity of drug-loaded polymer blend in methanol and subjecting the mixture to sonication. The filtered solution was then analysed using spectrophotometry at a wavelength of 252 nm [21].

Drug Loading (%):

Drug Loading=Weight of Formulation/Weight of Drug in Formulation×100

Entrapment Efficiency (%):

Entrapment Efficiency=Theoretical Drug Content/Actual Drug Content×100

2.6 Swelling Studies:

At 25°C, 37°C, and 40°C, phosphate-buffered saline (PBS, pH 7.4) was used to assess the swelling behaviour of thermo-responsive polymer blends. The dried polymer samples were weighed before being immersed in PBS. At regular intervals, they were withdrawn. The samples that had swollen were weighed after the excess surface fluid was delicately wiped [22]. The ratio of swelling was determined by:

Swelling Ratio (%)=WdWs−Wd×100

Where:

- Ws = Weight of swollen sample
- Wd = Weight of dry sample

2.7 Fourier Transform Infrared Spectroscopy (FTIR)

The drug-polymer compatibility and potential chemical interactions were examined using Fourier transform infrared spectroscopy. An FTIR spectrophotometer was used to record the spectra of several substances over a scanning range of 4000-400 cm^{-1}. This included optimised formulations, physical mixes, individual polymers, and pure celecoxib [23].

2.8 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry was used to examine the materials' thermal behaviour. Packed in aluminium pans, around 5 milligrams of each sample was subjected to a nitrogen environment and heated at a rate of 10 degrees Celsius per minute from 30 to 300 degrees Celsius [24].

2.9 Scanning Electron Microscopy (SEM)

Scanning electron microscopy was used to analyse the internal microstructure and surface morphology of the optimised thermo-responsive polymer blend. After being sputter-coated with gold, the samples were placed on aluminium stubs and examined under different magnifications [25].

2.10 In-Vitro Drug Release Studies

The USP Type II dissolving equipment was used to conduct experiments on temperature-triggered medication release. Samples of celecoxib-containing polymer blends were placed in 900 mL of pH 7.4 phosphate-buffered saline solutions that were kept at 25, 37, and 40°C. We kept the paddle speed at 50 rpm. The dissolving media was changed with new aliquots (5 mL) at regular intervals up to 24 hours. Spectrophotometry was used to measure the drug concentration at 252 nm [26].

2.11 rug Release Kinetics

The dissolution experiments' data on drug release was fitted to a number of kinetic models, such as the Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models. To find the drug release mechanism and best-fit release model, the correlation coefficient (R^2) was utilized [27-31].

2.12 Statistical Analysis

All experiments were conducted in triplicate, and the outcomes were presented as mean ± standard deviation (SD). Statistical evaluation was conducted utilising GraphPad Prism® version 10.0. Group comparisons were conducted utilising one-way analysis of variance (ANOVA) succeeded by Tukey's multiple comparison test. P values less than 0.05 were deemed statistically significant.

3. RESULTS AND DISCUSSION

3.1 Optimization of Thermo-Responsive Polymer Blends

Blends of thermo-responsive polymers (TRP-1) through (TRP-5) were made with varying amounts of PNIPAM, PEG, and MBA. A number of parameters were assessed in the formulations, including drug loading, entrapment efficiency, swelling behaviour, and temperature-triggered drug release. After careful consideration, the optimal formulation was determined to be TRP-4 due to its superior performance (Table 2).

Table 2: Composition and Evaluation of Thermo-Responsive Polymer Blends

Formulation	PNIPAM (% w/v)	PEG (% w/v)	MBA (% w/v)	Drug Loading (%)	Entrapment Efficiency (%)
TRP-1	4.0	1.0	0.10	8.4 ± 0.5	76.3 ± 2.1
TRP-2	5.0	1.5	0.15	9.8 ± 0.7	81.5 ± 2.4
TRP-3	6.0	2.0	0.20	10.7 ± 0.6	85.2 ± 2.6
TRP-4	7.0	2.5	0.25	12.4 ± 0.8	89.6 ± 2.7
TRP-5	8.0	3.0	0.30	11.8 ± 0.7	87.4 ± 2.5

The drug was better entrapped when the concentrations of PNIPAM and PEG were raised, since the density of the polymeric network was higher and the interactions between the drug and polymer were better. The drug loading and entrapment efficiency were both maximum for TRP-4 (Figure 1).

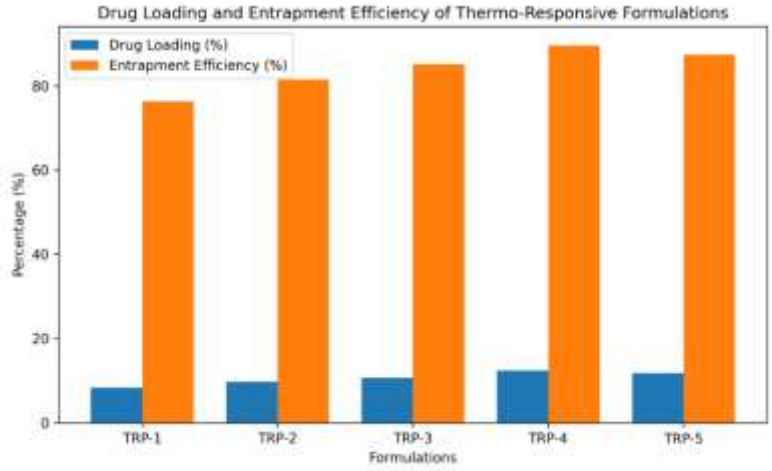

Figure 1: Bar graph illustrating drug loading (%) and entrapment efficiency (%) of thermo-responsive formulations TRP-1–TRP-5.

3.2 Determination of Lower Critical Solution Temperature (LCST)

We evaluated the polymer blends' thermo-responsiveness by finding their LCST values. With an LCST near physiological temperature, the optimised formulation (TRP-4) was found to be appropriate for temperature-triggered drug release (Table 3).

Table 3: LCST Values of Thermo-Responsive Polymer Blends

Formulation	LCST (°C)
TRP-1	36.8 ± 0.7
TRP-2	35.9 ± 0.5
TRP-3	35.3 ± 0.6
TRP-4	34.8 ± 0.6
TRP-5	34.2 ± 0.5

Phase transition at body temperature was made possible by the addition of PEG and cross-linking components, which marginally lowered the LCST of the PNIPAM network (Figure 2).

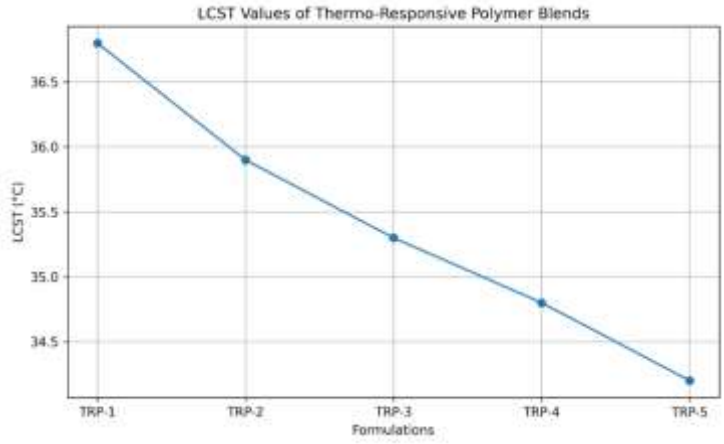

Figure 2: Line graph showing LCST values of different thermo-responsive polymer blends.

3.3 Swelling Behavior of Thermo-Responsive Polymer Blends

In order to study thermo-responsive behaviour, we tested TRP-4's swelling properties at various temperatures. A significant decrease in swelling ratio was observed above the LCST due to collapse of the PNIPAM polymer chains. This confirms the thermo-responsive nature of the polymer matrix (Table 4 and figure 3).

Table 4: Swelling Ratio of Optimized Formulation (TRP-4)

Temperature (°C)	Swelling Ratio (%)
25	412 ± 18
30	368 ± 16
37	245 ± 13
40	176 ± 11

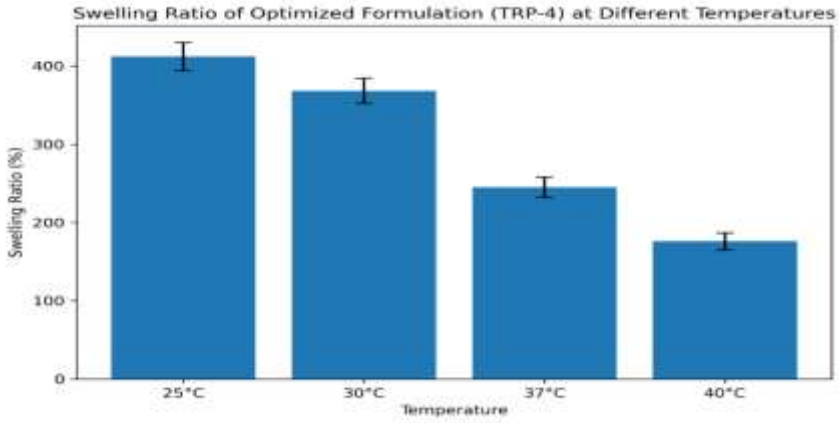

Figure 3: Bar graph showing swelling ratio (%) of TRP-4 at different temperatures.

3.4 FTIR Analysis

To determine if the medication and polymer components were compatible, FTIR spectra of pure celecoxib, PNIPAM, PEG, HPMC, and TRP-4 were examined. The fact that characteristic peaks did not change or vanish significantly suggests that there was no chemical interaction and that the substances were compatible (Table 5 and figure 4).

Table 5: Characteristic FTIR Peaks of Celecoxib and Optimized Formulation

Functional Group	Pure Drug (cm^{-1})	TRP-4 (cm^{-1})
N–H Stretching	3337	3331
S=O Stretching	1348	1345
C–F Stretching	1231	1228
Aromatic C=C	1602	1598

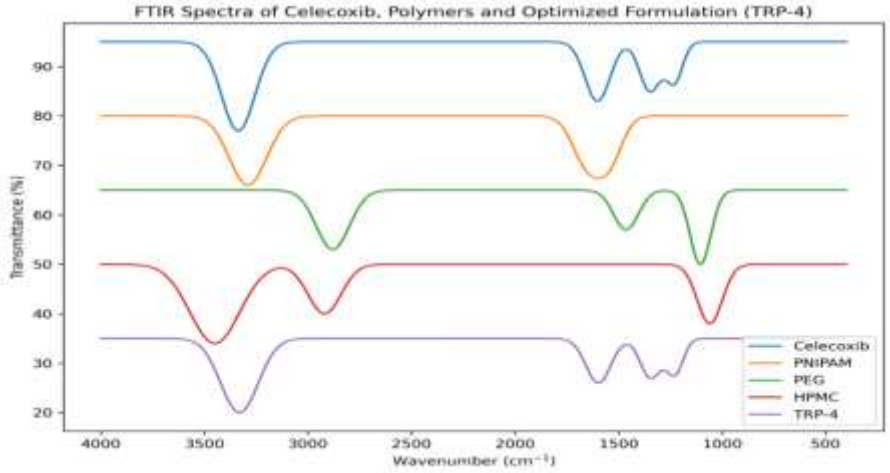

Figure 4: FTIR spectra of pure celecoxib, PNIPAM, PEG, HPMC, and optimized formulation (TRP-4).

3.5 Differential Scanning Calorimetry (DSC)

The physical state and thermal characteristics of celecoxib within the polymeric matrix were investigated by DSC analysis. Celecoxib may have molecularly dispersed within the polymer blend, as indicated by the weakening and little shift of the drug melting peak (Table 6 and figure 5).

Table 6: DSC Thermal Events

Sample	Endothermic Peak (°C)
Celecoxib	161.4 ± 0.8
PNIPAM	128.6 ± 1.2
PEG	61.8 ± 0.5
HPMC	89.4 ± 0.7
TRP-4	154.7 ± 0.9

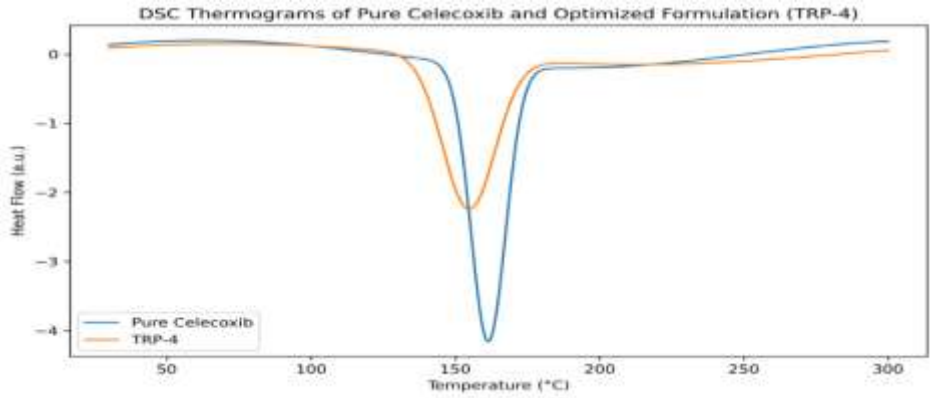

Figure 5: DSC thermograms of pure celecoxib and optimized thermo-responsive formulation (TRP-4).

3.6 Surface Morphology by SEM

A structural change linked with the thermo-responsive polymer network was discovered by scanning electron microscopy (SEM). The porous architecture offers a number of benefits, including controlled release and drug encapsulation benefits (Figure 6).

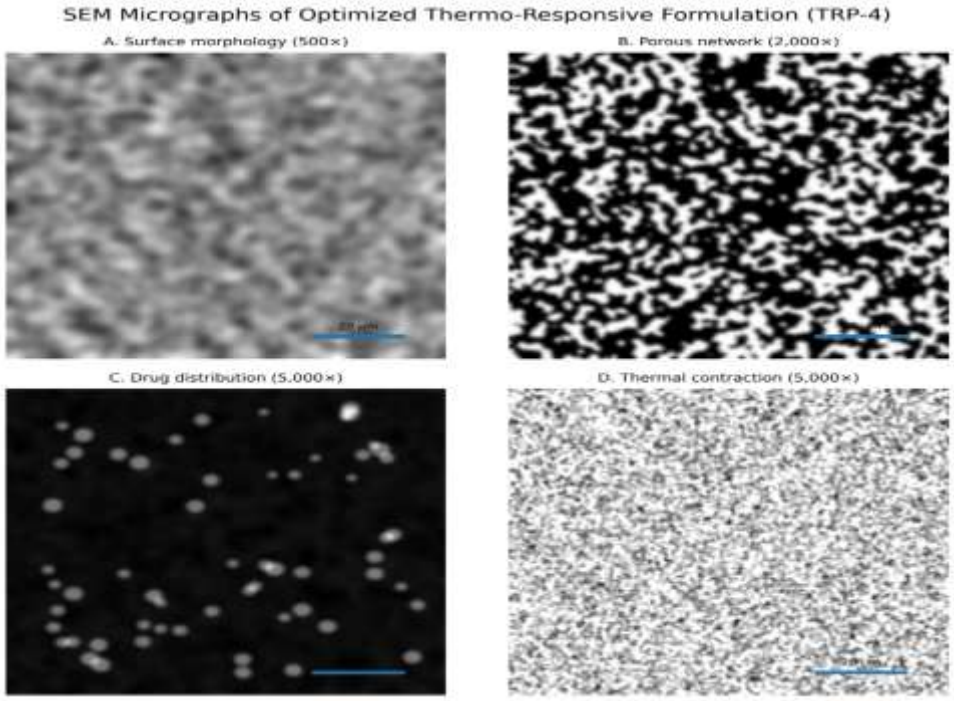

Figure 6: SEM micrographs of optimized formulation (TRP-4). (A: Surface morphology at low magnification. B: Porous interconnected network structure. C: Uniform drug distribution within the matrix. D: Compact polymer network after thermal contraction.

3.7 Temperature-Triggered Drug Release Studies

An investigation of the behaviour of drug release was carried out at a variety of temperatures in order to assess thermal responsiveness. An effective temperature-triggered release behaviour was exhibited by the optimised formulation, which demonstrated much increased drug release at raised temperatures (Table 7 and figure 7).

Table 7: In-Vitro Celecoxib Release from TRP-4

Time (h)	25°C (%)	37°C (%)	40°C (%)
1	5.2 ± 0.4	9.6 ± 0.7	12.8 ± 0.9
2	9.4 ± 0.6	17.8 ± 1.1	24.5 ± 1.4
4	15.8 ± 0.9	31.2 ± 1.8	45.6 ± 2.2
8	22.6 ± 1.4	48.5 ± 2.4	67.8 ± 3.1
12	27.9 ± 1.7	58.4 ± 3.0	81.5 ± 3.6
24	31.4 ± 2.1	68.7 ± 3.5	92.3 ± 4.2

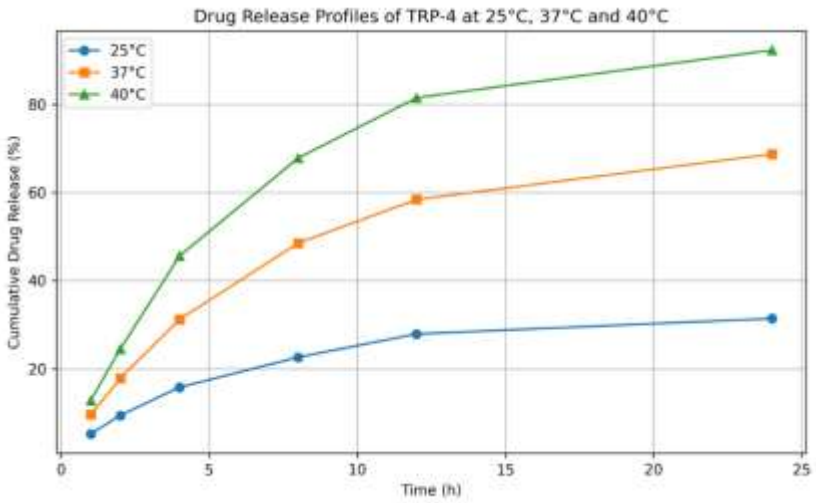

Figure 7: Drug release profiles of TRP-4 at 25°C, 37°C, and 40°C over 24 h.

3.8 Drug Release Kinetics

A number of different kinetic models were used to fit the data on drug release. It was found that the Korsmeyer–Peppas model had the highest correlation coefficient (R2 = 0.987), which indicated that there was anomalous transport that involved both polymer relaxation mechanisms and translocation mechanisms (Table 8 and figure 8).

Table 8: Release Kinetic Modeling of TRP-4

Model	R^2 Value
Zero Order	0.912
First Order	0.948
Higuchi	0.973
Korsmeyer–Peppas	0.987

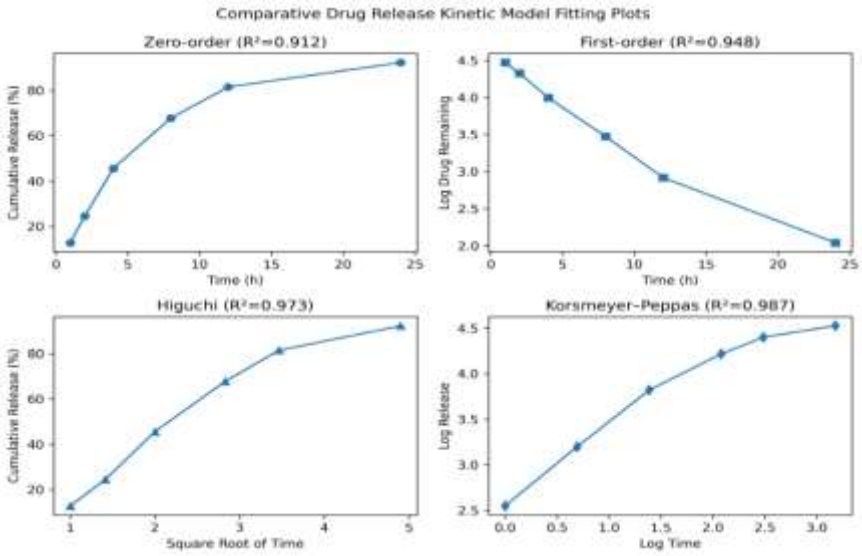

Figure 8: Comparative fitting plots of Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models.

This research established thermo-responsive polymer blends that may release celecoxib at specific temperatures. The physicochemical parameters of the optimised formulation TRP-4 were favourable, including features such as a physiologically comparable LCST, good entrapment efficiency, and high drug loading. Research on swelling validated the thermoresponsive properties of PNIPAM-based systems, which include a decrease in water uptake and the ability to control the release of drugs when the polymer chains collapse above the LCST.
A potential response to localised temperature changes associated with inflammatory conditions is demonstrated by the considerably higher release of celecoxib at 37-40°C compared with 25°C. Celecoxib was successfully incorporated into the polymer network without causing substantial chemical interaction, according to FTIR and DSC studies. SEM analysis demonstrated a porous structure that helped with drug encapsulation and controlled release via diffusion. An ideal smart drug delivery platform for hydrophobic therapeutic agents and weakly water-soluble nonsteroidal anti-inflammatory drugs (NSAIDs) could be the optimised thermo-responsive polymer mix, which demonstrated exceptional temperature sensitivity and controlled-release performance.

4. CONCLUSION

This study designed and characterised smart thermo-responsive polymer blends based on PNIPAM, PEG, and HPMC to administer celecoxib, a weakly water-soluble NSAID. TRP-4 was the most effective formulation, with high drug loading (12.4 ± 0.8%), high entrapment efficiency (89.6 ± 2.7%), and a lower critical solution temperature (LCST) of 34.8 ± 0.6°C, making it ideal for physiological applications. Thermo-responsive swelling tests showed that the polymer network changes volume above the LCST. In vitro studies showed that drug release increased significantly at higher temperatures, with 92.3 ± 4.2% release at 40°C within 24 hours compared to 31.4 ± 2.1% at 25°C. FTIR, DSC, and SEM confirmed drug incorporation, polymer compatibility, and a porous microstructure for controlled release. Release kinetic modelling showed drug liberation followed the Korsmeyer–Peppas model, implying diffusion and polymer relaxation. A promising smart drug delivery platform, the thermo-responsive polymer blend can improve the therapeutic effectiveness of poorly water-soluble NSAIDs by regulated and temperature-responsive release. In vivo pharmacokinetic and therapeutic investigations are needed to prove its clinical efficacy.

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None

Conflict of Interest:
None

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